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International application number: PCT/GB05/000800

International filing date: 04 March 2005 (04.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: GB
Number: 0405009.2
Filing date: 05 March 2004 (05.03.2004)

Date of receipt at the International Bureau: 02 May 2005 (02.05.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

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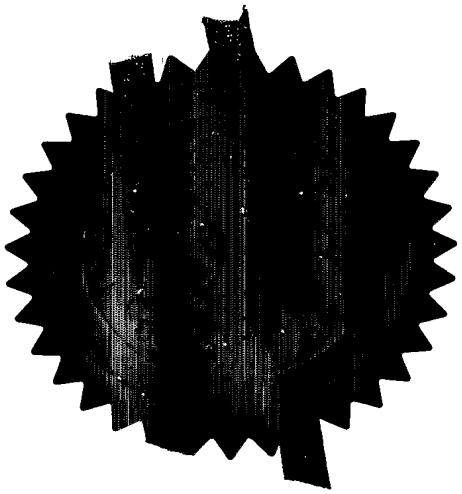

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Dated 4 April 2005

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1. Your reference: 47627.GB01/NT

2. Patent application number *(The Patent Office will fill in this part)*: 05 MAR 2004 0405009.2

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*:
Cambridge Biotechnology Ltd
P.O. Box 230
Cambridge
CB2 1XJ
United Kingdom

Patents ADP number *(if you know it)*: 08208761002

If the applicant is a corporate body, give the country/state of incorporation: United Kingdom

4. Title of the invention: Analgesics

5. Full name, address and postcode in the United Kingdom to which all correspondence relating to this form and translation should be sent:
Reddie & Grose
16 Theobalds Road
LONDON
WC1X 8PL

Patents ADP number *(if you know it)*: 91001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application *(if you know it)*	Date of filing *(day/month/year)*

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Number of earlier application	Date of filing *(day/month/year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
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11. I/We request the grant of a patent on the basis of this application.

Signature: Reddie & Grose

Date: 5 March 2004

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47627.GB01

Analgesics

This invention relates to analgesic compounds and to methods of preventing, treating, or ameliorating pain using these compounds.

Pain has two components, each involving activation of sensory neurons. The first component is the early or immediate phase when a sensory neuron is stimulated, for instance as the result of heat or pressure on the skin. The second component is the consequence of an increased sensitivity of the sensory mechanisms innervating tissue which has been previously damaged. This second component is referred to as hyperlagesia, and is involved in all forms of chronic pain arising from tissue damage, but not in the early or immediate phase of pain perception.

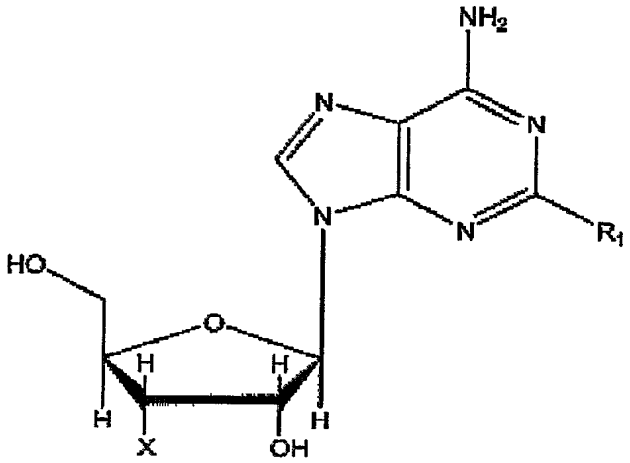
Thus, hyperalgesia is a condition of heightened pain perception caused by tissue damage. This condition is a natural response of the nervous system apparently designed to encourage protection of the damaged tissue by an injured individual, to give time for tissue repair to occur. There are two known underlying causes of this condition, an increase in sensory neuron activity, and a change in neuronal processing of nociceptive information which occurs in the spinal cord. Hyperalgesia can be debilitating in conditions of chronic inflammation (e.g. rheumatoid arthritis), and when sensory nerve damage has occurred (i.e. neuropathic pain).

Two major classes of analgesics are known: (i) non steroidal anti-inflammatory drugs (NSAIDs) and the related COX-2 inhibitors; and (ii) opiates based on morphine. Analgesics of both classes are effective in controlling normal, immediate or nociceptive pain. However, they are less effective against some types of hyperalgesic pain, such as neuropathic pain. Many medical practitioners are reluctant to prescribe opiates at the high doses required to affect neuropathic pain because of the side effects caused by administration of these compounds, and the possibility that patients may become addicted to them. NSAIDs are much less potent than opiates, so even higher doses of these compounds are required. However, this is undesirable because these compounds cause irritation of the gastro-intestinal tract.

Adenosine A1 receptor agonists are known to act as powerful analgesics (Sawynok, Eur J Pharmacol. (1998) 347, 1-11), and adenosine A2A receptor agonists are known to act as anti-inflammatory agents. However, development of adenosine-based therapies has generally been precluded because they have unacceptable side effects. Selective A1 receptor agonists cause bradycardia, and A2A receptor agonists cause widespread vasodilation with consequent hypotension and tachycardia.

There is, therefore, a need to provide analgesics, particularly anti-hyperalgesics, which are sufficiently potent to control pain perception in neuropathic and other hyperalgesic syndromes, and which do not have serious side effects or cause patients to become addicted to them.

According to the invention there is provided adenosine receptor agonists of the following formulae:

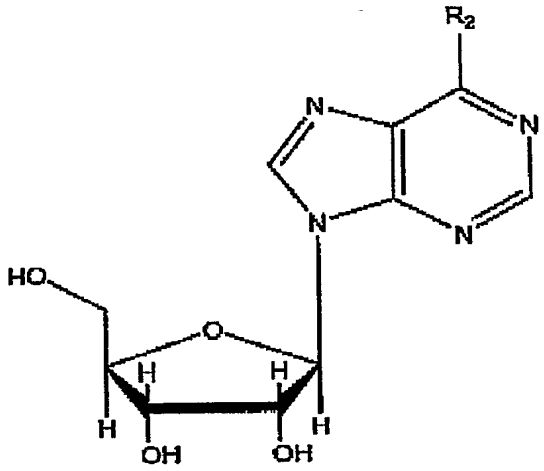


(I)

wherein:

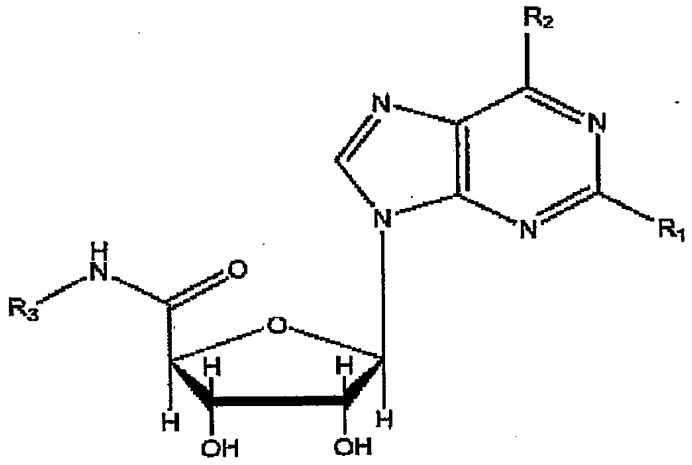
when X = OH, R_1 is C_1 or C_4-C_6 alkoxy, phenoxy, substituted phenoxy (preferably substituted with nitrile, phenyl or 3-isopropyl), (5-indanyl)oxy, C_1, C_2, C_5, or C_6 alkylamino (straight chain or cyclic), phenylamino, phenylamino with either methoxy or fluoro substituents, (N-methyl, N-isoamylamino), a C_2 sulfone group, a C_7 alkyl group, or OCH_2CH_2OH; or

when X = H, R_1 is *n*-hexyloxy;



(II)

wherein R_2 is NMe_2, N-(2-isopentenyl), piperazinyl, (N-Me, N-benzyl) or (N-Me, N-(2-methoxyethyl));



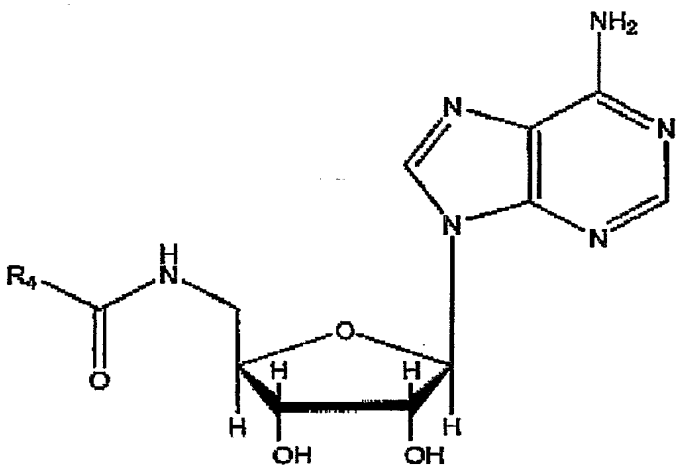
(III)

wherein:

when R_1 = H, R_3 is an isopropyl group, and R_2 is either NH_2 or a methylamino group (NHMe); or

when R_1 = H, R_3 is H, and R_2 is NH_2; or

when R_1 is OMe, R_3 is Ph, and R_2 is NH_2;



(IV)

wherein R_4 is *n*-propyl or $NHCH_2CH_3$.

It is believed that compounds of formulae (I)-(IV) have analgesic activity and can be administered with reduced probability and severity of side effects compared to other adenosine receptor agonists:

According to the invention there is provided use of a compound of formula (I), (II), (III), or (IV) in the manufacture of a medicament for the prevention, treatment, or amelioration of pain, particularly hyperalgesia.

There is also provided according to the invention a method of preventing, treating, or ameliorating pain (particularly hyperalgesia) which comprises administering a compound of formula (I), (II), (III), or (IV) to a subject in need of such prevention, treatment, or amelioration.

Preferred compounds of formula (I), (II), (III), and (IV) are detailed in the Examples.

Compounds of formulae (I)-(IV) are believed to be effective in inhibiting pain perception in mammals suffering from pain, in particular neuropathic or inflammatory pain, even when administered at doses expected to give plasma concentrations well below those known to activate adenosine receptors. Therefore, it is believed that compounds of formulae (I)-(IV) can treat pain (particularly neuropathic and inflammatory pain) without causing the significant side effects associated with administration of other adenosine receptor agonists.

As mentioned above hyperalgesia is a consequence in most instances of tissue damage, either damage directly to a sensory nerve, or damage of the tissue innervated by a given sensory nerve. Consequently, there are many conditions in which pain perception includes a component of hyperalgesia.

According to the invention there is provided use of a compound of formula (I), (II), (III), or (IV) as an analgesic (particularly an anti-hyperalgesic) for the prevention, treatment, or amelioration of pain (particularly hyperalgesia) caused as a result of neuropathy, including Diabetic Neuropathy, Polyneuropathy, Cancer Pain, Fibromyalgia, Myofascial Pain Syndrome, Osteoarthritis, Pancreatic Pain, Pelvic/Perineal pain, Post Herpetic Neuralgia, Rheumatoid Arthritis, Sciatica/Lumbar Radiculopathy, Spinal Stenosis, Temporo-mandibular Joint Disorder, HIV pain, Trigeminal Neuralgia, Chronic Neuropathic Pain, Lower Back Pain, Failed Back Surgery pain, back pain, post-operative pain, post physical trauma pain (including gunshot, road traffic accident, burns), Cardiac pain, Chest pain, Pelvic pain/PID, Joint pain (tendonitis, bursitis, acute arthritis), Neck Pain, Bowel Pain, Phantom Limb Pain, Obstetric Pain (labour/C-Section), Renal Colic, Acute Herpes Zoster Pain, Acute Pancreatitis Breakthrough Pain (Cancer), Dysmenorhoea/Endometriosis.

According to the invention there is also provided use of a compound of formula (I), (II), (III), or (IV) as an analgesic (particularly an anti-hyperalgesic) for the prevention, treatment, or amelioration of pain (particularly hyperalgesia) caused as a result of inflammatory disease, or as a result of combined inflammatory, autoimmune and neuropathic tissue damage, including rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis, and other arthritic conditions, cancer, HIV, chronic

pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury (including damage caused to organs as a consequence of reperfusion following ischaemic episodes e.g. myocardial infarcts, strokes), autoimmune damage (including multiple sclerosis, Guillam Barre Syndrome, myasthenia gravis) graft v. host rejection, allograft rejections, fever and myalgia due to infection, AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis, irritable bowel syndrome, osteoporosis, cerebral malaria and bacterial meningitis, bowel pain, cancer pain, back pain, fibromyalgia, post-operative pain.

The amount of a compound of the invention that is administered to a subject should be an amount which gives rise to a peak plasma concentration that is less than the lowest EC50 value of the compound at adenosine receptors (i.e. less than the lowest EC50 value of the compound at A1, A2A, A2B, and A3 adenosine receptors). Preferably the peak plasma concentration of the compound is one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the lowest EC50 value.

Preferably the amount of a compound of the invention that is administered gives rise to a plasma concentration that is maintained for more than one hour at one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the lowest EC50 value of the compound at adenosine receptors.

For the avoidance of doubt, the EC50 value of a compound is defined herein as the concentration of the compound that provokes a receptor response halfway between the baseline receptor response and the maximum receptor response (as determined, for example, using a dose-response curve).

The EC50 value should be determined under standard conditions (balanced salt solutions buffered to pH 7.4). For EC50 determinations using isolated membranes, cells and tissues this would be in buffered salt solution at pH 7.4 (e.g. cell culture medium), for example as in Tilburg *et al* (J. Med. Chem. (2002) *45*, 91-100). The EC50 could also be determined *in vivo* by measuring adenosine receptor mediated responses in a normal healthy animal, or even in a tissue perfused under normal conditions (i.e. oxygenated blood, or oxygenated isotonic media, also buffered at pH 7.4) in a normal healthy animal.

Alternatively, the amount of a compound of the invention that is administered may be an amount that results in a peak plasma concentration that is less than the lowest or highest Kd value of the compound at adenosine receptors (i.e. less than the lowest or highest Kd value of the compound at A1, A2A, A2B, and A3 adenosine receptors). Preferably the peak plasma concentration of the compound is one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the lowest or highest Kd value.

Preferably the amount of the compound that is administered is an amount that results in a plasma concentration that is maintained for more than one hour at one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the lowest or highest Kd value of the compound at adenosine receptors.

The Kd value of the compound at each receptor should be determined under standard conditions using plasma membranes as a source of the adenosine receptors derived either from tissues or cells endogenously expressing these receptors or from cells transfected with DNA vectors encoding the adenosine receptor genes. Alternatively whole cell preparations using cells expressing adenosine receptors can be used.

Labelled ligands (e.g. radiolabelled) selective for the different receptors should be used in buffered (pH7.4) salt solutions (see e.g. Tilburg et al, J. Med. Chem. (2002) 45, 420-429) to determine the binding affinity and thus the Kd of the compound at each receptor.

Alternatively, the amount of a compound of the invention that is administered may be an amount that is one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the minimum amount of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered. Preferably the amount administered gives rise to a plasma concentration that is maintained for more than one hour at one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the minimum amount of the compound that gives rise to the side effects.

Alternatively, the amount of a compound of the invention that is administered may be an amount that gives rise to plasma concentrations that are one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the minimum plasma concentration of the compound that cause bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered. Preferably the amount administered gives rise to a plasma concentration that is maintained for more than one hour at one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth,

or one fiftieth to one fifth, or one tenth to one fifth) of the minimum plasma concentration of the compound that causes the side effects.

It is expected that the amount of a compound of the invention that is administered should be 0.001-15 mg/kg. The amount may be less than 6 mg/kg. The amount may be at least 0.001, 0.01, or 0.1 mg/kg. The amount may be less than 0.1, or 0.01 mg/kg. Preferred ranges are 0.001-10, 0.001-5, 0.001-2, 0.001-1, 0.001-0.1, 0.001-0.01, 0.01-10, 0.01-5, 0.01-2, 0.01-1, 0.1-10, 0.1-5, 0.1-2, 0.1-1, 0.2-1.2, 0.2-1, mg/kg.

Preferred doses for a 70kg human subject are less than 420mg, preferably at least 0.7mg, more preferably at least 3.5mg, most preferably at least 7mg. More preferably 7-70mg, or 14-70mg.

It is believed that the dosage amounts specified above are significantly lower (up to approximately 1000 times lower) than would be expected to be required for an analgesic effect based on the EC50 value of the compound at the adenosine A2A receptor.

The appropriate dosage of a compound of the invention will vary with the age, sex, weight, and condition of the subject being treated, the potency of the compound, and the route of administration, etc. The appropriate dosage can readily be determined by one skilled in the art.

A compound of the invention may be administered with or without other therapeutic agents, for example analgesics or anti-inflammatories (such as opiates, steroids, NSAIDs, cannabinoids, tachykinin modulators, or bradykinin modulators) or anti-hyperalgesics (such as gabapentin, pregabalin, cannabinoids, sodium or calcium channel modulators, anti-epileptics or anti-depressants).

In general, a compound of the invention may be administered by known means, in any suitable formulation, by any suitable route. A compound of the invention is preferably administered orally, parenterally, sublingually, transdermally, intrathecally, or transmucosally. Other suitable routes include intravenous, intramuscular,

subcutaneous, inhaled, and topical. The amount of drug administered will typically be higher when administered orally than when administered, say, intravenously.

It will be appreciated that a compound of the invention may be administered together with a physiologically acceptable carrier, excipient, or diluent.

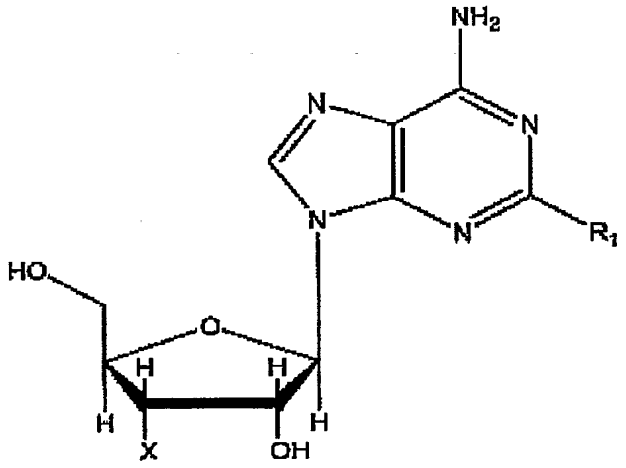
Suitable compositions, for example for oral administration, include solid unit dose forms, and those containing liquid, e.g. for injection, such as tablets, capsules, vials and ampoules, in which the active agent is formulated, by known means, with a physiologically acceptable excipient, diluent or carrier. Suitable diluents and carriers are known, and include, for example, lactose and talc, together with appropriate binding agents etc.

A unit dosage of a compound of the invention typically comprises up to 500 mg (for example 1 to 500 mg, preferably 5 to 500 mg) of the active agent. Preferably the active agent is in the form of a pharmaceutical composition comprising the active agent and a physiologically acceptable carrier, excipient, or diluent. The preferred dosage is 0.1 to 2, e.g. 0.5 to 1, typically about 0.2 or 0.6, mg of the active agent per kg of the (human) subject. At these levels, it is believed that effective treatment can be achieved substantially without a concomitant fall (for example, no more than 10%) in blood pressure.

Preferably a compound of the invention is administered at a frequency of 2 or 3 times per day.

Structures of preferred compounds of the invention are given in the Examples below. A Ki value is given for each compound. To calculate this, rat striatal membranes were incubated for 90 minutes at 22°C in the presence of 2nM [3H]-CGS21680, 1Unit/ml adenosine deaminase and increasing concentrations of the compound being studied, prior to filtration and liquid scintillation counting.

Example 1



When X = OH

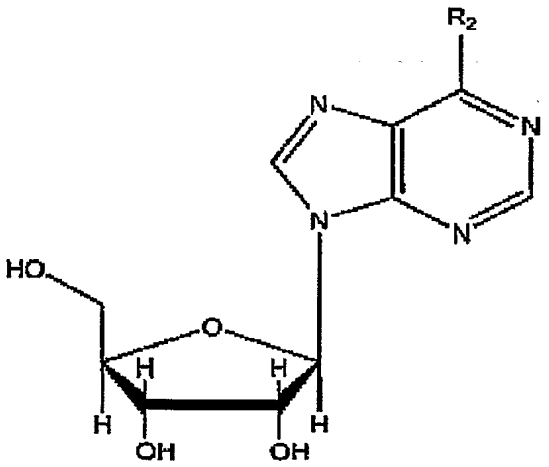
Compound No.	Structure R_1	(Ki) nM
1	OCH3	1300
2	$OCH_2CH_2CH_2CH_3$	280
3	O $CH_2CH_2CH_2CH_2CH_2CH_3$	1500
4	OPh	2500
5	O-(4-cyano)Ph	1300
6	O-(3-Ph)Ph	620
7	5-indanyloxy	760
8	O-(3-$CH(CH_3)_2$)Ph	560
9	$NH(CH_3)$	1356
10	$NHCH_2CH_3$	1200
11	$N(CH_3)_2$	13350
12	$NHCH_2CH_2CH_2CH_2CH_2CH_3$	290
13	NHPh	160
14	NH-(4-MeO)Ph	55
15	NH-(4-F)Ph	200
16	NH-cyclopentyl	420
17	NH-cyclohexyl	1000

18	N-CH_3, N-$CH_2CH_2CH(CH_3)_2$	4000
19	OCH_2cyclopentyl	200
20	$SO_2CH_2CH_3$	39000
21	OCH_2CH_2OH	203
22	$CH_2CH_2CH_2CH_2CH_2CH_2CH_3$	800

When X = H

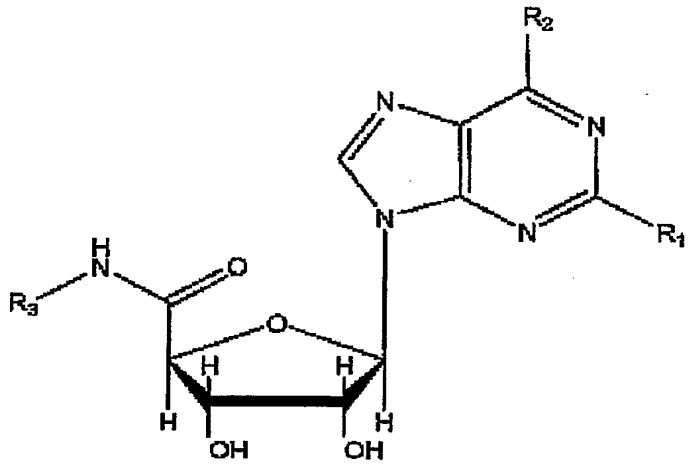
Compound No.	Structure R_1	(Ki) nM
23	O $CH_2CH_2CH_2CH_2CH_2CH_3$	2990

Example 2



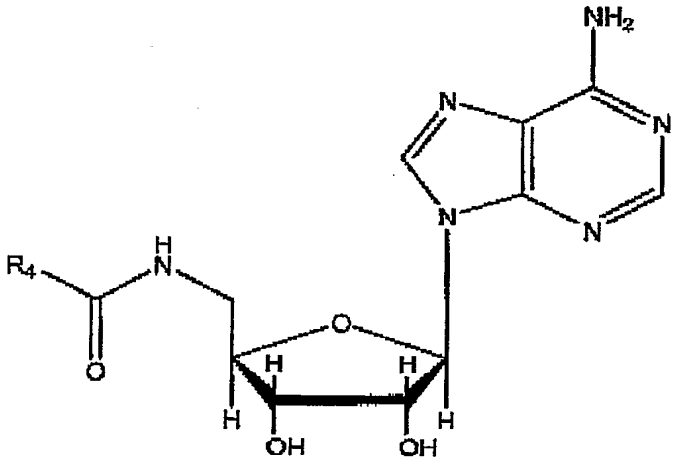
Compound No.	Structure R_2	(Ki) nM
24	$N(CH_3)_2$	450000
25	$NHCH_2CHC(CH_3)_2$	8600
26	$N\text{-}CH_3$, $N\text{-}CH_2Ph$	18500
27	Piperazinyl	5000
28	N-Me, $N\text{-}(CH_2CH_2OCH_3)$	13000

Example 3



Compound No.	R_1	R_2	R_3	(Ki) nM
29	H	NH_2	$CH(CH_3)_2$	1930
30	H	NH_2	H	270
31	H	$NHCH_3$	$CH(CH_3)_2$	2440
32	OCH_3	NH_2	Ph	26100

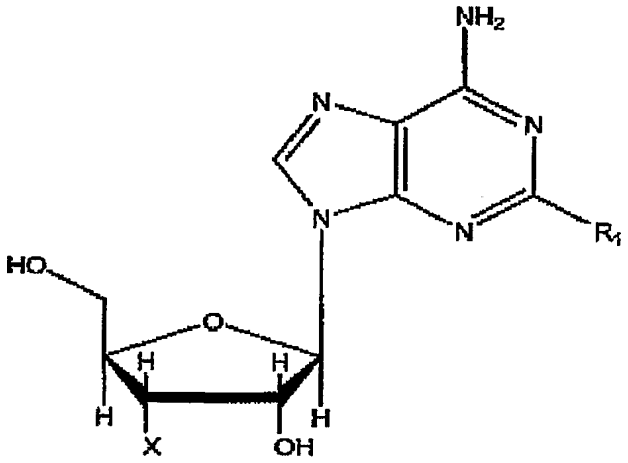
Example 4



Compound No.	Structure R_4	(Ki) nM
33	$CH_2CH_2CH_3$	16900
34	$NHCH_2CH_3$	6570

Claims

1. A compound of formula (I), (II), (III), or (IV):

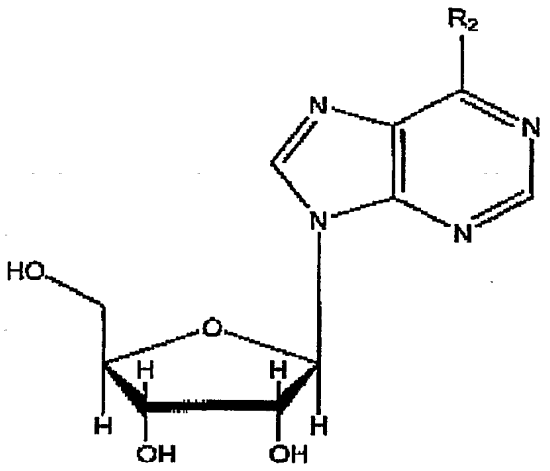


(I)

wherein:

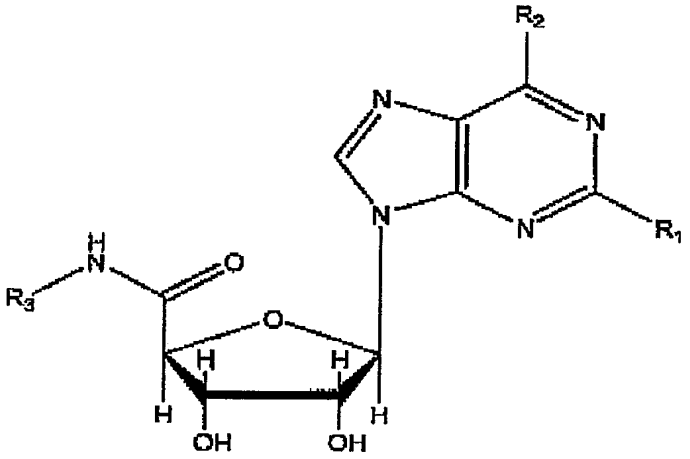
when X = OH, R_1 is C_1 or C_4-C_6 alkoxy, phenoxy, substituted phenoxy (preferably substituted with nitrile, phenyl or 3-isopropyl), (5-indanyl)oxy, C_1, C_2, C_5, or C_6 alkylamino (straight chain or cyclic), phenylamino, phenylamino with either methoxy or fluoro substituents, (N-methyl, N-isoamylamino), a C_2 sulfone group, a C_7 alkyl group, or OCH_2CH_2OH; or

when X = H, R_1 is *n*-hexyloxy;



(II)

wherein R_2 is NMe_2, N-(2-isopentenyl), piperazinyl, (N-Me, N-benzyl) or (N-Me, N-(2-methoxyethyl));



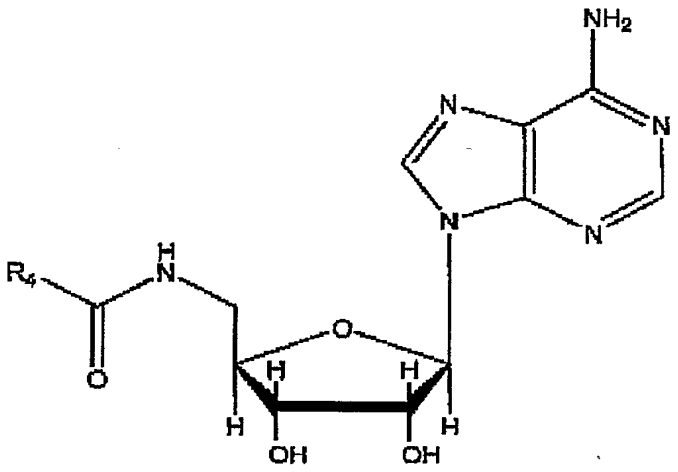
(III)

wherein:

when R_1 = H, R_3 is an isopropyl group, and R_2 is either NH_2 or a methylamino group (NHMe); or

when R_1 = H, R_3 is H, and R_2 is NH_2; or

when R_1 is OMe, R_3 is Ph, and R_2 is NH_2;



(IV)

wherein R_4 is *n*-propyl or $NHCH_2CH_3$.

2. A compound according to claim 1 with a structure as defined in any of Examples 1-4.

3. A compound according to claim 1 or 2 for use as a medicament.

4. Use of a compound according to claim 1 or 2 in the manufacture of a medicament for the prevention, treatment, or amelioration of pain.

5. Use according to claim 4, wherein the pain is hyperalgesia.

6. Use according to claim 5, wherein the hyperalgesia is neuropathic pain.

7. Use according to any of claims 4 to 6 for the prevention, treatment, or amelioration of: pain associated with cancer, pancreatic pain, pelvic/perineal pain, pain associated with HIV infection, chronic neuropathic pain, lower back pain, failed back surgery pain, back pain, post-operative pain, post physical trauma pain, cardiac pain, chest pain, pelvic pain/PID, joint pain, neck pain, bowel pain, phantom limb pain, obstetric pain, acute herpes zoster pain, acute pancreatitis breakthrough pain, or for the prevention, treatment, or amelioration of neuropathic or other pain caused by,

or associated with diabetic neuropathy, polyneuropathy, fibromyalgia, myofascial pain syndrome, osteoarthritis, post herpetic neuralgia, rheumatoid arthritis, sciatica/lumbar radiculopathy, spinal stenosis, temporo-mandibular joint disorder, trigeminal neuralgia, renal colic, dysmenorhoea/endometriosis.

8. Use according to claim 5, wherein the hyperalgesia is inflammatory pain.

9. Use according to any of claims 4, 5, or 8 wherein the pain is caused by or associated with an inflammatory or immune disease, or as a result of combined inflammatory, autoimmune and neuropathic tissue damage.

10. Use according to any of claims 4, 5, 8, or 9 for the prevention, treatment, or amelioration of bowel pain, pain associated with cancer, back pain, post-operative pain, or for the prevention, treatment, or amelioration of inflammatory or other pain caused by, or associated with rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis, cancer, HIV, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, autoimmune damage, graft v. host rejection, allograft rejections, fever and myalgia due to infection, fibromyalgia, AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis, irritable bowel syndrome, osteoporosis, cerebral malaria and bacterial meningitis.

11. A method of preventing, treating, or ameliorating pain which comprises administering a compound according to claim 1 or 2 to a subject in need of such prevention, treatment, or amelioration.

12. A method according to claim 11, wherein the compound is administered to the subject in an amount that results in a peak plasma concentration of the compound in the subject that is one ten thousandth to one fifth of the lowest EC50 value of the compound at adenosine receptors.

13. A method according to claim 11 or 12, wherein the compound is administered to the subject in an amount that results in a plasma concentration of the compound in

the subject being maintained for more than one hour at one ten thousandth to one fifth of the lowest EC50 value of the compound at adenosine receptors.

14. A method according to any of claims 11 to 13, wherein the compound is administered to the subject in an amount that results in a peak plasma concentration of the compound in the subject that is one ten thousandth to one fifth of the lowest Kd value of the compound at adenosine receptors.

15. A method according to any of claims 11 to 14, wherein the compound is administered to the subject in an amount that results in a plasma concentration of the compound in the subject being maintained for more than one hour at one ten thousandth to one fifth of the lowest Kd value of the compound at adenosine receptors.

16. A method according to any of claims 11 to 15, wherein the compound is administered to the subject in an amount that is one ten thousandth to one fifth of the minimum amount of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is administered.

17. A method according to any of claims 11 to 16, wherein the compound is administered to the subject in an amount that results in a plasma concentration of the compound in the subject being maintained for more than one hour at one ten thousandth to one fifth of the minimum plasma concentration of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is administered.

18. A method according to any of claims 11 to 17, wherein the compound is administered at a dosage of 0.001 to 6 mg/kg.